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Promising Interactions Between Psychiatry and Medicine

Herbert Weiner
Sidney Hart

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Herbert Weiner and Sidney Hart

Introduction

In every culture, the theory and practice of medicine is partly the product of its belief systems. In our culture, the education of the physician and the resulting practice of medicine is heavily influenced by the data of the biological and physical sciences, while at the same time commonly held attitudes—e.g., toward sickness, the complaints of the sick person, and old age—bias the daily interchange between doctor and patient, and, therefore, the practice of medicine.

In no way do we intend to deride the enormous advances in our understanding of disease mechanisms that have come about as the result of advances in biology. Nor do we wish to cast doubt on the need for more knowledge about human biology further to strengthen the rational underpinnings of the practice of medicine. For it is quite clear in retrospect that an understanding, e.g., of the pathophysiology of disease processes, can ultimately lead to their reversal by treatment.

In fact, medicine has a very strong intellectual appeal to most physicians because of the deep understanding of disease processes that the great advances in biology have provided them. But the theory and practice of medicine encompass much more than an understanding of basic physiological, physicochemical, and biochemical mechanisms. For example, the prevention of illness is much more effective than its treatment. To prevent an illness requires a rather full account of its etiology and pathogenesis, as well as an understanding of the social, economic, psychological, and political factors that may play proximal or distal roles in its etiology. However, most of medicine and medical education is predicated on knowledge and teaching about disturbances in body physiology and biochemistry *after* the inception of the disease—e.g., the nature of disturbances in electrolyte and water metabolism in primary aldosteronism or in adrenal-cortical insufficiency, or the fall in cardiac output in some cases of congestive heart disease. Treatment is directed at these disturbances, and not at their etiologic and pathogenetic causes, or the general circumstances under which the illness occurred. No distinction is made between disease and illness, illness being the result of the interaction of disease and its host—the person.

In this chapter, we offer evidence that the base of medical theory and practice needs to be broadened, in part to achieve a biological foundation for it in which man is seen in continuous interaction with his environment. As the result of this interaction, devices in the brain that control and regulate bodily

processes are brought into play. These neural devices are in open-loop interaction with other neural processes that transduce experiences that result from the organism's interaction with its environment. In stating this we do not overlook the presence of closed-loop regulatory and control processes that operate in the body with no apparent input from the outside world. In the past, the medical scientist has largely studied these closed-loop processes and has concluded that these are the only ones worthy of or feasible to study.

Unfortunately, and in practice, there is a strong belief that an understanding of the disturbed mechanism, after the inception of disease, provides us with a full explanation of the disease itself. We physicians tend, for instance, not to ask what it is that brought about the disturbance in the first place. Nor does such understanding tell us much about the sick human being.

For example, in the case of infectious diseases for which we have the most complete, conceptual model of pathogenesis, the question is rarely asked why one and not another type of pneumococcus "caused" the pneumonia, or why the pneumonia occurred at that particular time in the patient's life. The emphasis tends to be placed on the relative roles of the pathogenicity of the organism, and the factors that govern host resistance to it, as well as on the pathological changes wrought in the lung.

Furthermore, the fact that antibiotics rapidly arrest the disease process and the knowledge that penicillin interferes with bacterial cell-wall formation by the inhibition of mucopeptides, satisfies the physician that he has a complete picture of the disease and its cure. But what if the patient refuses to leave his bed when all signs and symptoms of the pneumonia have disappeared? An understanding of the pathophysiology and pathology of pneumonia does not provide him with an understanding of the patient's behavior.

Such a banal, yet relatively common, occurrence in the practice of medicine highlights the current belief systems, and the conceptual issues that tend to permeate the practice of medicine.

These belief systems are the result of a longstanding tradition in Western life that holds that man is a machine, and that a full knowledge of man can only be furthered by an increasingly refined quantitative analysis of his complex machinery. Such an analysis requires that complex phenomena be reduced to increasingly simple elements, which can be analyzed by available scientific techniques.

This process of analysis has been highly successful for *simple systems,* but when we deal with *complex* phenomena such an analysis is not usually successful. It is, of course, entirely true that great scientific advances have

been made by the analytic method, a fact that is used to support the argument that it is the *only* method to use in the exploration of natural phenomena. There is indeed much evidence that the greatest scientific advances have been made by an analysis of model systems of a simple, and not of a complex nature: Bohr's model of atomic structure, achieved in part by his quantization of mechanical motion, pertains to the hydrogen, not the uranium atom. Sherrington deduced important central, neural processes from his study of the spinal reflex and not from studying complex behavior. The control and regulation of protein synthesis has been worked out in bacteria, not in animal cells or colonies of cells.

There is, however, another Western belief system that holds that man is only in part matter and that there are distinct and clearly definable differences between mind and matter. Descartes pointed out that matter was extended in time and space whereas mind or soul was not. He insisted on the absolute independence of mind and matter (body): the body was a machine and animals had only bodies and were mere machines.

Descartes' dualism still has a powerful hold on Western thought. The study of mind has become a major activity in the past seventy years and has been introduced into medical education and practice in the form of psychiatry. Because of the nature of its subject matter, the scientific limitations on the acquisition of data about one's own and other's minds, and

the particular attitudes that the practice of psychiatry generates in other medical men, psychiatry has, to a very large extent, remained outside the mainstream of medicine.

To specify: first, the central problem in the study of mind is the problem of consciousness. Its study continues to remain wholly outside the realm of science, despite the fact that Descartes was wrong and that it is a good bet, according to ethologists, that at least some of the higher mammals, in addition to man, must be capable of consciousness. Therefore, animals cannot merely be machines.

Secondly, many behavioral scientists believe that there are such serious limitations on the reliability and validity of observations about one's own and other people's minds, that the study of the mind is worthless. Behavioral scientists of this persuasion believe, in addition, that man is only a machine, a passive automaton controlled by his environment,[1] and that only behavior and its course can be quantified.

Such behavioral scientists are, therefore, very much of the same philosophic persuasion as those who have limited the scientific method only to quantitative measurement and simple elements. Unfortunately, the belief systems of the behaviorists (already described) lead them to speak of the "control" and shaping" of behavior by reward or reinforcement, or,

regretfully, even persuasion. Implicit in this goal is the startling fact that the subject must attain and maintain some behavior that another has in mind for him. In the case of the patient with pneumonia, he must willy-nilly leave his bed and return home: scientific psychology has become moral philosophy.

It is a fact that the kind of attitude toward the patient that has just been described is one that also permeates most of medical practice. The fact that it does is a cause of continual misunderstanding between practicing physicians and psychiatrists. Among most physicians there is an attitude, which, in part, stems from their scientific belief systems and, in part, from their training, that one does not share one's medical knowledge with patients and that one gives treatment *to* them, directed mainly at the disturbed mechanism *within* them. Most psychiatrists have learned, however, that in dealing with patients the most effective manner is to work *with* them in a "therapeutic" alliance. In fact, there is evidence that a major cause of anxiety in patients, and one that can produce acute changes in physiological functioning, is an ambiguous situation such as that caused by the patient not being told what is wrong with him, the nature of his medication, the severity and prognosis of his disease, etc.

If the physician, furthermore, only sees his patient as a machine, he, the mechanic, will be the subject of behavior that stands in direct opposition to the humane tradition in medicine. If he cannot fix the machinery, he will abandon it: A phenomenon daily observed in physicians caring for the dying

patient. If he is ultra-scientific, he sees himself as coldly objective and removed from the patient, who, in turn, feels himself rejected by the physician.

It is, however, not our purpose to write a polemic about the clay feet of physicians, but rather to point out that current belief systems in medicine have inevitable consequences for the behavior of the physician; furthermore, that such behavior may be stressful to the patient.

The study of stress in the past twenty years is, in actuality, highly relevant to the practice and theory of medicine. It has been brought to such a state of knowledge that it is possible to document today that stressful situations may have very important physiological consequences for the organism. The onset of disease may be one of the consequences of stress. To understand why a stress may lead to disturbed physiology and—even disease in one person and not another—one must have knowledge of a patient's genetic endowment and previous experiences.

We have chosen this topic to illustrate how psychiatry, as a behavioral science, can productively interact with medicine in contributing to an understanding of the etiology, pathogenesis, and pathophysiology of disease. Such an interaction can also influence patient care and may point to new directions in medical education.

There are, therefore, a number of possible causes of misunderstanding that might occur among psychiatrists and others in medicine. These arise to a very large degree because of the differences in attitudes toward patients, and in hypotheses about the pathogenesis of disease.

Much of American psychiatry is of the "dynamic" variety: it seeks the cause of psychological illness—especially the neuroses—in conflictual, unconscious motivations within man. And this model of the pathogenesis of neurotic symptoms has been extended to psychosomatic relationships. But it is very difficult on brief observation to infer and verify the existence of such motivations in the person being observed. Demonstrating them, therefore, to the skeptical physician is either very difficult or unconvincing, with the result that further misunderstanding is generated between the physician and the psychiatrist.

But there has also been a shift in emphasis in psychiatry because of the development of a broader perspective on human behavior and psychological functioning. Man's behavior is no longer seen as the mere product of psychological conflict but rather is viewed in a broader biological context as the result of complex interactions between genetic endowment and the environment in which the child grows up. Among these interactions are those of the growing child and his family, peers and culture. The historical period in

which he is raised may also be of determining influence. The impact of these experiences on his mind, and their storage, "programs" him to react toward others and specific situations in his life in a manner similar to or identical with ways first learned in childhood. In respect to the practice of medicine, he may, as an adult, when ill, react to and interact with the physician in terms of his experiences as a child with his pediatrician, and with his parents when he was ill and what being ill meant to him when he was young.

Studies on Attachment and Loss

During childhood very strong attachments to others are also formed. Such bonds have been observed to occur in other mammals, and their importance to the well-being of the organism is highlighted when they are broken.

The breaking of a bond between human beings may have one of several consequences. The usual manner in which man psychologically reacts is with grief, which is then gradually dispelled by the process of mourning. On the other hand, he may react with depression and suicide, with helplessness or hopelessness, or even elation, or with behavior called schizophrenic, or he may "drown" his feelings in alcohol or "forget" with other drugs. Loss of another person may lead to the development of a wide variety of physiological effects and anatomic lesions: it is a setting in which peptic

duodenal ulcer, for example, may occur.

Real or threatened loss has also been cited by many authors as a factor contributing to the precipitation of various other disease states. These include cancer,'' tuberculosis, ulcerative colitis, diabetes mellitus, and thyrotoxicosis,' etc. Schmale, postulating that object loss and depression are often the setting in which disease occurs, studied forty-two patients, selected for age (eighteen to forty-five years) and to some extent for social class, who were admitted to a general medical service with diagnoses ranging from hysterical conversion symptoms to aseptic meningitis. Shortly after admission each patient was interviewed using the conventional, open-ended, psychiatric interview. Special attention was paid to a history of loss or change in relationship with a highly valued object, and the nature of the loss was operationally divided into four categories: (1) actual loss, (2) threatened loss, (3) "symbolic" loss, and (4) no loss. In sixteen cases of the forty-two, the patient either reported or the investigator inferred that a loss, or significant change in relationships to others had occurred within twenty-four hours of the appearance of symptoms of the disease. In another fifteen patients, such loss or change occurred within the week prior to the onset of illness. Thus, thirty-one of forty-two patients experienced the onset of an illness within one week of a significant loss. Another eight patients gave a similar history for the month prior to the onset of illness. Schmale also noted that thirty-five of the forty-two patients experienced real or threatened loss in the first sixteen years of their lives.

Many of these persons had unresolved conflicts with respect to these events, which were rekindled by their present illness. In a later study, Adamson and Schmale noted that object loss and "giving-up" were associated with the development of severe psychiatric disturbance. Recently, Stein and Charles reported that almost half of the juvenile diabetics they studied in an adolescent clinic had a history of loss of one or both parents. This was in marked contrast to the experience of a group of matched controls, comprised primarily of adolescents with hematological disorders. As a result of their data Stein and Charles concluded that "diabetes occurs most frequently in that segment of the population in which there are special stresses and trauma in the form of a chaotic family life, separations, and early losses."

Young et al., studying the mortality among widowers, found that 213 of 4486 widowers, fifty-five years old and older, died within the first six months of the loss of their spouse, an increase of about 40 percent above that expected for married men of the same age. Kraus and Lilienfeld noted that the mortality rate of persons of both sexes, who had lost a spouse, was increased and that there was a mortality in excess of that expected in those under thirty-five years of age. Parkes in a study of patients admitted to a psychiatric hospital found that the number of patients whose illness followed the loss of a spouse was significantly greater than anticipated for people of that age and social group. Developing Schmale's work in the area of giving-up and its primary feelings of hopelessness and helplessness, Engel has hypothesized

that the "giving-up, given-up complex" is the emotional setting in which disease occurs. He estimates that this "complex" precedes the onset of illness in 70 to 80 percent of patients. As with all stressful stimuli, Engel notes that it is difficult to appreciate which external stimuli will be critical to a particular person: the determining factor will be how the individual responds—that is to say, just what constitutes a loss or threatened loss will depend upon the individual's past experience and present capacity for dealing with loss. Where a serious loss is suffered or threatened, the predisposed person may react by giving-up, leading to a state of having given-up. The most characteristic feature of this is the sense of "psychological impotence"—a feeling that for a period of time one is unable to cope with any task. Clinically, the complex is manifested by (1) the feelings of helplessness and hopelessness; (2) low self-esteem; (3) an inability to enjoy the company of other people, one's work, hobbies, etc.; (4) a disruption of the sense of continuity in one's past, present, and future; and (5) a reactivation of memories of earlier periods of giving-up. Engel believes that this state of mind may last for varying periods of time, and that it is commonplace for people to experience this complex several times during a lifetime; in situations in which prompt resolution is impossible and periods of "struggling" alternate with periods of giving-up, illness may occur.

Additional evidence for the point of view that there are psychological antecedents to illness has been forthcoming: Perlman et al. recently reported a relationship between violent arguments with, or threatened separations

from, family members and the precipitation of congestive heart failure. Kennedy and Bakst studied patients admitted for cardiac surgery to see if their preoperative psychological state would influence the morbidity and mortality of operation. They established six categories of psychological state:

1. Patients who evidenced strong but not psychotic denial of the operation and were strongly motivated to recover.

2. While manifestly cooperative and seemingly motivated, another group of patients had settled comfortably into dependency on others and the benefits of being disabled. Postoperatively they tended to experience little or no improvement in cardiac function.

3. Another group of patients was increasingly panicky as the day of surgery approached. They tended to exaggerate the risks of the procedures and were afraid of dying.

4. Patients who tended to have mixed feelings about surgery, in that they preferred to be ill rather than well.

5. Patients who had effectively given up all hope and perceived surgery as “sanctioned suicide” that the surgeon committed for them.

6. Patients with overt psychiatric illness who exaggerated their relatively minor physical illness into a major one.

The authors found that the postoperative morbidity and mortality were

highest in patients in categories 2., 4., and 5. Kimball confirmed these findings in a separate study, emphasizing the negative correlation between depression in his patients and successful surgical outcome.

As yet we do not know what mechanisms lie behind the correlations just described: most of the behavioral biology of depressive states and psychological disorganization has been worked out with psychiatric patients while studying adrenal-cortical and medullary hormones. In 1963 Sachar et al. reported data from longitudinal studies of four patients with acute schizophrenic reactions. There was a statistically reliable correlation between acute states of panic and disruption of most psychological functions and elevated urinary 17-hydroxycorticoids (17-OIICS), epinephrine, and norepinephrine. Peak values occurred during the acute state of emotional turmoil at the onset of the psychosis. With the appearance of an elaborate and well-formed delusional system, hormone levels returned to normal for a period of time, only to rise again when the patient was confronted with the reasons for his breakdown (such as the breaking-off of a relationship). During the recovery phase, urinary 17-OHCS, epinephrine, and norepinephrine returned to normal. More relevant to our discussion are the studies' with depressive patients that have revealed the same findings. Sachar emphasizes that just as the well-organized delusional system serves to restore internal equilibrium and protect the patient from extremes of anxiety in schizophrenic illness, so does the *apparent* agitation and misery serve to protect the

depressed patient from the pain of loss and mourning. Studying six acutely depressed women in an inpatient setting, Sachar and his co-workers made longitudinal studies of urinary 17-OHCS levels and correlated these with observations of the patient's behavior. They postulated that if depressive symptoms actually protected the patient against the realization of loss, confronting her with the loss should provoke psychological "disequilibrium" and result in the rise in the excretion level of 17-OHCS. Indeed, this was what happened. Using more sophisticated techniques, Sachar and his colleagues conclude that ". . . adrenocortical activity in depressed patients is primarily related to dimensions of emotional arousal and psychotic disorganization rather than to depressive illness *per se"* or to schizophrenia. This conclusion applied to the observations of Schmale and Engel suggests that the emotional consequences of the loss—the "giving-up, given-up" complex—is the result of a failure of "coping" mechanisms, leading, on the one hand, to the psychological reactions described and, on the other hand, to physiological change, including physical illness. Since the perceived threat of stress results in the increased secretion of ACTH (adrenocorticotropic hormone) and cortisol, and since these hormones are known to have wide-ranging effects on a variety of systems and functions (electrolyte balance, glucose and fat metabolism, nitrogen excretion, the induction of the biosynthetic enzyme of epinephrine, immune mechanisms, and the electrical excitability of brain tissue, etc.) the possible effects of this form of stress on the onset of disease

may be rooted, in part, in this physiological system.

Of particular interest is the work that has related psychological defenses and other coping mechanisms, as intervening variables in the perception of an event in the environment and its interpretation by man as a threat. One may well wonder why it is that although the five manifestations of the giving-up, given-up complex described by Engel are experienced singly or in combination by large numbers of people in response to stressful experiences throughout their lifetime, most people deal with these experiences without becoming ill.

Hamburg—in a paper exploring how the search for and the utilization of information in the course of major life transitions serves coping behavior—cited seventeen stressful, everyday experiences. These events range from separation of children from their parents to the threat of war, or war itself. He lists other common experiences such as illness, the birth of siblings, going to school, puberty, marriage, pregnancy, the birth of children, and migration. Hamburg notes that most of the psychiatric literature has emphasized the use of "defenses" to avoid the impact or minimize the mental pain of such experiences. But experiences do not have to be threatening. In fact, Hamburg has devoted much effort to the study of other more successful adaptive means of coping with new and/or stressful situations, so as to allow for their integration into the life experience of the people involved. In soldiers who

have suffered severe burns, Hamburg noted that they tended, at first, to deny or minimize the nature and extent of the injury and its probable consequences, but that later a gradual transition occurred allowing them to accept the injury and their own rehabilitation. Eventually, such patients come to terms with the realities of their situation, their prospects for recovery, the potential limitations on their future lives: periods of depression and discouragement are regularly observed during this period. When permanent disability results, the coping process is aided by a sense of belonging to a "special" group. An opportunity for a badly burned patient to discuss with a physician his concerns about the injury and its consequences occasionally resulted in a dramatically improved outlook. In an effort to relieve their distress and difficulty, some patients are prepared to face certain facts and to make use of them in a way that they avoided previously . Thus, the seeking and' utilizing of information provided by another person may be useful to some patients as a means of coping with injury.

This was true of the parents of children dying from leukemia who were studied by Wolff et al. After an initial period of shock, disbelief, and depression on being told about their child's illness, these parents gradually came to accept it by inquiring about it. Their sense of responsibility for the illness could be dispelled by a frank discussion of its nature, by information about treatment and, finally, by advice and sympathy concerning the anticipated loss of their child.

At each stage of this process, Wolff and his colleagues accurately predicted the 17-OHCS levels in the parents. Their criteria for predicting these levels were the "integrity" of inferred psychological defenses (such as repression, denial, isolation, identification, etc.) and the extent of emotional arousal (especially of unpleasant feelings).

They studied the characteristic differences among individual parents with the hypothesis in mind that the more effectively a person defends himself against impending loss, the lower will be his mean 17-OHCS excretion rate. In twenty-three of the thirty-one instances, predictions were made from the psychological data obtained of the levels of 17-OHCS excretion; the results supported the hypothesis that the more "effective" the defenses, the lower the mean 17-OHCS excretion level. Therefore, one of the implications of this study is that the baseline level of an individual's 17-OHCS excretion level may reflect the general "effectiveness" of "ego" defenses.

Bourne et al. pursued this line of investigation by studying seven helicopter and ambulance medics who were evacuating combat casualties. They found their subjects' mean twenty-four-hour urinary, 17-OHCS-excretion level remained relatively constant from day to day, whether or not they were flying rescue missions. Their mean level of steroid excretion was considerably lower than that anticipated on the basis of their body weights, when compared with a group of trainees at Fort Dix. On the psychological

side, one may conclude that an adaptation to a dangerous situation had occurred with a correlated lowering of steroid excretion levels, whereas in their comparison group of trainees, no such adaptation had taken place. It may, therefore, be that in an acutely stressful situation excretion levels are high, but that as psychological adaptation occurs they fall.

After the development of techniques for measuring cortisol production rates (rather than excretion levels), Katz et al. found that in a group of women anticipating breast biopsy the correlation of psychological-criteria measures similar to those employed by Wolff et al. worked better with production rate than with excretion levels. Women who showed the greatest emotional distress or experienced such unpleasant feelings as fear, dejection, despair, or apprehension tended to have relatively elevated hydrocortisone production rates, while those who were more hopeful or accepting showed relatively low rates.

Other forms of loss may be correlated with changes in body biochemistry by mechanisms still unknown. Kasl, Cobb, and Brooks reported a longitudinal study of changes in serum uric acid (SUA) and cholesterol levels in men undergoing job loss. The subjects were fifty-six married men, thirty-five to sixty years of age, who had held blue-collar jobs for a minimum of three years, and who were about to lose them because of a permanent plant shutdown. They were seen by public health nurses approximately three

months before and then one, four, eight, twelve, and twenty-four months after they lost their jobs. On each visit, blood and urine specimens were collected, blood pressure, pulse, height, and weight were measured, and a structured interview schedule administered for the purpose of collecting various social, psychological, and health data. Thirty-four control subjects who came from plants that were continuing to operate were also studied in the same way.

The principal findings in this study were: (1) Anticipation of plant shutdown was associated with elevated SUA but normal cholesterol levels; (2) SUA levels rapidly dropped back to premorbid levels if new employment was quickly found; otherwise, they tended to remain elevated until reemployment; (3) the more "stressful" the men found the period of anticipated job loss, the greater was the change in SUA level; (4) those men who did not wait for their jobs to be terminated but resigned in order to seek new jobs had high stable SUA levels; (5) cholesterol levels did not rise while the loss of a job was anticipated but rose during the period of unemployment, returning to previous levels only after a new job was found; and (6) members of the control group showed no significant fluctuations either in serum uric acid or cholesterol levels during the period of study.

In 1967 and 1968, Bahe and co-workers' reported a study in which SUA and cholesterol levels were measured three times weekly in thirty-two men undergoing training in a navy Underwater Demolition Team (UDT). These

exercises are considered to be among the most “rigorous . . . and stressful” training experiences in military life. The subjects were picked randomly from a UDT class and observed until they either successfully completed the course or withdrew. The behavioral data was obtained by means of clinical interviews and a psychological questionnaire prepared by Holmes and Rahe.

The investigators found statistically significant ($p < 0.025$) elevations in mean SUA level on mornings when the subjects were eagerly preparing to take on new, challenging and often physically complicated UDT activities. A significant fall in mean serum uric acid levels occurred on days of prolonged, tedious, and unpleasant physical activity, or when the schedule was unusually light. These fluctuations were more dramatic in the group of twenty men who successfully completed the course than in the twelve who did not. In general, SUA levels were higher and cholesterol levels lower in those who mastered the course most successfully. Serum cholesterol levels generally tended to fluctuate in the opposite direction from SUA levels. Illustrative of this pattern were the changes that occurred during the first week of training when the men were most enthusiastic, alert, and generally confident of their abilities to cope with the task at hand; at this time, group mean SUA level was at its highest (7.78 mg. percent) and cholesterol level near its lowest value. By the time the training course was almost over, the enthusiasm of the participants had waned considerably as the task had become mechanically routine but physically overwhelming. During this period, SUA levels fell to relatively low

levels (mean=5.46 mg. percent) while cholesterol levels reached their peak.

The authors concluded that, in response to dire conditions, elevations in SUA levels had occurred in their subjects. However, while it is probably incontrovertible that training for underwater demolition is stressful, for any stress to be genuinely distressing to the stressed individual, it must be perceived as a threat. Thus, one might suspect that for someone who viewed successful completion of the UDT course as a personal challenge (i.e., someone who is a "striver") this situation might indeed represent a potential threat. However, the authors present relatively little information as to the precise emotional impact of this experience on the different individuals in the study and do not discuss this in relation to individual differences in SUA fluctuations.

In the closing paragraph of the second paper, Rahe et al. suggested that an analysis of serum cortisol levels in these subjects might reveal further interesting relationships between SUA, cholesterol, and cortisol under "stressful" conditions. Rubin, Rahe, and coworkers did go on to publish these data in 1969 and 1970 and their reports' provide information potentially relevant to the pathogenesis of gout. They found that, while their subjects tended to run chronically elevated serum cortisol levels, further significant but transient elevations of serum cortisol also occurred. These took place in periods apparently characterized by *anxious* (rather than enthusiastic)

anticipation of training situations that promised to be exceedingly demanding. Since, for many subjects, situations that were likely to evoke anxious anticipation alternated with those associated with enthusiastic optimism about the task, SUA and cortisol levels were frequently out of phase with each other, i.e., one would be falling while the other was rising, or vice versa.

This finding may be of importance in the light of a report in 1946 by Heilman that acute gouty arthritis had occurred in previously asymptomatic hyperuricemic subjects following the termination of a course of ACTH.

It had also been shown by Heilman that corticosteroids have, in addition to their anti-inflammatory action, the capacity to increase uric acid excretion by the kidneys. Thus, a precipitous decline in relatively elevated serum cortisol level could conceivably result in a rebound elevation (via the kidneys) in SUA level; this might then be associated with an attack of acute gouty arthritis.

Lest we be misunderstood, we are *not* saying that loss of another person by death or separation, or loss of a job is the only cause of illness or of physiological changes. We are saying that given a certain kind of genetic endowment (such an endowment probably plays a part in serious depressive illness, gout, peptic ulcer, etc.) *and* certain kinds of life experiences that

sensitize the individual to react in his own particular manner to loss, loss may play a role in a variety of kinds of illnesses. In other words, some percentage of the etiologic and/or pathogenetic variance of the illness is accounted for by the setting in which the illness occurs, loss being a particular potent setting for profound behavioral and physiological consequences in the predisposed. We also say that in the evaluation of serum levels or production rates of biochemical or hormonal variables, one must take into account the psychological state of the person, in the same manner that we take into account his posture, or at what time of the day (that is, when during the circadian cycle) the blood samples are taken.

Effect of Separation on Young Mammals

We have emphasized that early experiences of separation and loss may sensitize human beings to later losses. In view of the fact that a confirmation of this hypothesis would require an (unethical) prospective study, it has been tested in higher mammals by several groups of investigators. In these animals profound, immediate behavioral consequences ensue consisting of marked motor activity, pitiful crying, sleep disruption that gradually merges into immobility and very characteristic species-specific postures. The long-range effects of separating young animals from their mothers on their adult behavior have also been studied: every aspect of behavior—social, reproductive, maternal, aggressive—is affected.

In these studies, in which young animals have been separated from their mothers, her offspring usually treated her disappearance as a complex experience that could be compensated for by surrogate mothering. In these experiments no attempt was made to analyze the individual effects on the infant of nutritional, olfactory, tactile, auditory, visual, or thermal stimuli after separation. The absence of such an analysis makes it impossible to determine whether changes in or deprivation of these simpler forms of stimulation do not produce the observed effects. Because prematurely separated young animals eat less and lose weight, their food intake is possibly the most critical, uncontrolled variable in these experiments. Deprivation of sensory inputs and litter size may also affect the development of young animals. Hofer, using rats, found that the critical variables that intervene in the effect of separation of fourteen-day old rat pups from their mothers are the mother's milk, and, in part, an unfamiliar environment. He is also the first investigator to study the *physiological* effect of separation: It produced a 40 percent drop in heart and respiratory rate during the first twelve to sixteen hours after separation. Hofer also showed that it is the absence of the mother's milk that produces the separation effect on these rats. Milk fed by stomach tube to fourteen-day old rats, left without food for sixteen hours after being separated from their mothers, transiently but fully reversed the decrease in heart rate that had occurred. The effect is rapid, produced by all three of the major chemical components of milk, and is related to the amount of milk given, but not to

gastric filling or distention. The effect of increasing heart rate by milk seems to depend on ^-adrenergic transmission on the effector side. However, the afferent arc in the loop that mediates the nutritional effects on heart rate and the central nervous mechanisms by which milk sustains heart and respiratory rates remain unknown. The questions one might ask are: What are the afferent neural pathways, or what substance in milk sustains these rates? Or does the absence of milk produce changes in important neurochemical mediators in the brain? This last question is not far-fetched in view of the fact that there are known long-term effects of lowered protein intake on brain dopamine, norepinephrine, and tyrosine hydroxylase levels in the perinatal period. What still remains is to determine the short-term effects on brain amines of nutritional deprivation following separation. If such an effect is shown, different amounts of nutrition or different nutritional substances could be manipulated to determine dose-response relationship between food intake, brain-amine levels, and heart rate.

The effects of separation on the behavior of rat pups studied singly are an increase in activity and a greater tendency to rear up on their hind legs. When studied in groups of four, there is more self-grooming, more defecation, and urination, and a decreased tendency to enter REM sleep.

Stress Research and Its Implications for Medical Care

So far we have emphasized work or loss as an important stress that may play a role in the inception of illness and in producing physiological changes. The knowledge derived from such studies has implications for medical care. For example, the doctor can act as a surrogate for a bereaved spouse or child. He can aid the grieving person in the process of mourning. He can support a bereaved person to ameliorate the psychophysiological consequences of loss. If he knows that a patient has suffered a loss, he will not label elevated levels of SUA, etc. as "idiopathic."

There are, however, many other stressful events that may occur in a patient's life. These include the ambiguity of not knowing the diagnosis and prognosis of his illness, the indifference of the physician, the anticipation of surgery, treatment by special technical procedures such as renal dialysis, and being put in intensive- or cardiac-care units.

Elsewhere in this *Handbook* (see Volume 4, Chapters 1 and 2) these topics are discussed at length.

Other Socioeconomic Variables in Disease and Illness

We have emphasized the role of separation or loss in human life as the prototype of the kind of social situation that may be correlated with behavioral and physiological changes. Separation may have its most profound effects early in a child's life and, again, in old age. As far as we know the

effects of separation transcend membership in any one social class; but, here again, too little information is available: social isolation, as a form of separation, has been (probably incorrectly) thought to be an important variable in the pathogenesis of schizophrenia; members of the lowest socioeconomic class in cities are most exposed to such isolation.

Separation may occur through death, migration, divorce, by children growing up and moving away. It may be caused by political unrest, genocide, and war. In these situations, separation becomes the critical intervening variable between the individual and the particular historical era in which he lives. The obverse situations—political and economic stability, and a stable social structure—may be particularly conducive to the prevention of disease. A study done over a period of twelve years demonstrated that in Roseto, Pennsylvania, the death rate from myocardial infarction was less than one-half that in neighboring communities or in the United States as a whole. Obesity, smoking, and other risk factors for myocardial infarction were all present in the population. The relatives of the inhabitants of Roseto who lived elsewhere had as high an incidence of infarction as the rest of the population of the United States. The only variable that could account for the discrepancy in incidence was that Roseto had an unusually cohesive social structure, with no poverty or crime, with great civic pride, and a tradition of mutual help to neighbors in need. The family structure was patriarchal and the elders of the community continued to participate in its affairs.

Work such as this suggests that the social structure of a community does play a role in averting disease. One may not casually conclude the obverse, however, For example, even under the most dire conditions such as those of a Nazi concentration camp, the incidence of peptic ulcer and bronchial asthma was said to be very low. Oppression and discrimination may play an additional and marked role in disease. The incidence of hypertension, and, in particular, its malignant phase, is much higher in American blacks than in whites or in African blacks.

Factors other than social ones may play a role in the etiology of essential hypertension. Unknown in New Guinea, it is a major cause of death in Japan; relationships between elevated blood pressure and the dietary content of salt have been sought to explain these observations which indicate an interaction of diet, culture, and disease.

Socioeconomic factors may play a role in the pathogenesis of disease. Overcrowding, economic hardship, job loss, and poor housing conditions, etc. may expose urban inhabitants to lead poisoning, rat bites, and rat-borne diseases, etc. The life in the city may prove stressful to those from rural areas, and vice versa. For some, success, marriage, or parenthood may prove a hardship and precipitate illness. An important variable is the rapidity with which political, social, or economic change occurs, even if this change appears to be personally salubrious or desirable: In our particular historical era, there

is a “crisis in leadership” in which previously, much sought-after academic, industrial, and political roles have become increasingly difficult and upsetting for those who assume them.

In addition to the actually stressful aspects of social change or the assumption of particular roles, each individual perceives and reacts to these in his own manner: some adapt to the perception of the event and some do not. For this reason, we believe that disease is an adaptive failure, and that any one factor—be it social, political, nutritional, or infectious—is not *the* cause of the disease itself. The factors mentioned may, furthermore, interact with each other to make the adaptive task more difficult.

The view that disease is an adaptive failure to situations and experiences that either are actually adverse or are perceived as such and thus constitute a threat, and that disease is not the *direct* result of these factors themselves, differs from the conceptual model most physicians maintain. If we hold a minority view, it behooves us to demonstrate that stress and threat do indeed bring about a variety of bodily changes and to show the reader the mechanism of such change, when known. It is to this end that the subsequent material in this chapter is presented. This material has mainly been obtained by research on animals. It verifies the data already reviewed.

The Effects of Stress on Physiological Function

Hormonal Variables

Most physicians are not accustomed to the language of the behavioral sciences and they tend to dismiss the observations of behavioral scientists, psychiatrists, and medical sociologists as unreliable. There are, indeed, many methodological problems that await research in these areas. And observations made retrospectively on patients about the settings in which their illness began are often contaminated by such variables as the effects of hospitalization, and of the illness on the patient. However, when patients are selected at risk for, but prior to the onset of, an illness, the data becomes more convincing. When this is not possible, a test of hypotheses can be made on animal subjects.

We now present data to show that stress indeed has potent effects on physiological variables. From Mason we learn that there are, in all likelihood, neural and neuroendocrine mechanisms that regulate the orderly and sequential release of hormones in animals under stress. During and following a seventy-two-hour period when a monkey is actively engaged in avoiding shock, some hormone levels rapidly rise while levels of other hormones decline, and the change in levels of still others far outlast any avoidance session. For example, he has shown that urinary 17-hydroxycorticosteroid and epinephrine levels are elevated during an avoidance session. After the session, levels of the former decline slowly, and the latter rapidly.

Norepinephrine levels in urine rise during the session, continue to rise after it and remain elevated for at least six days thereafter. Thyroid responses rise slowly and then fall during and after the session. Insulin levels rise only after the session, consequent to showing a slight dip during and immediately after it. Male and female sex hormones and the volume of urine excreted tend to be depressed during and for, at least, one day after the experimental procedure.

In other words, with some variations in amounts and pattern among monkeys, avoidance conditioning causes an organized pattern of hormonal release. This work does not tell us what regulates such release, nor what it is specifically in the experimental situation that sets the regulatory devices into motion As Mason has pointed out, there are several elements involved, among them sleep deprivation, the muscular activity entailed in lever pressing, the visual stimulus of the warning light, tactile and proprioceptive feedback when the lever is manipulated, the mild pain of electrical shock when the lever is not pressed, and the novelty of the experimental situation. With cogent argument, Mason discounts the importance of these factors. He believes that the prepotent stressful factor, the critical intervening variable in the experimental situation, is the emotional disturbance associated with the avoidance behavior.

Mason's demonstration of an organized pattern of hormonal release raises the question of how such a pattern comes about. In all likelihood, the

changes in catecholamine levels are at first neuronally mediated, but later hormonal and neuronal mechanisms play a part in their elevation. We do not know what regulates the particular change in sex-hormone levels. One might ask if the stress of avoidance conditioning actually causes a decline of pituitary-trophic hormones or whether the suppression of sex-hormone levels is due to a decreased production in testis, ovary, or adrenal gland. If so, how does this come about?

The patterns of the release that Mason has studied are, with some likelihood, in part determined by hypothalamic and adrenal transducer cells. It remains to be determined by what neural circuits and mechanisms these cells are linked to mechanisms responsible for the emotional disturbance that is, in Mason's opinion, the critical intervening variable.

In the meantime, however, we have learned that these integrated patterns of hormone release are analyzable into separate components. For example, the biosynthesis of the catecholamines in the adrenal gland is under several separate mechanisms. These include long-term hormonal control by ACTH over three of the enzymes involved in the biosynthesis of the catecholamines, and short- and long-term neural control and regulation of the same enzymes.

That such separate mechanisms obtain is implicit in Mason's work. The

novelty of the chair in which the monkey sits prior to an avoidance session produced immediate effects on hormone levels not dissimilar to those produced by the experimental procedure. Furthermore, when the avoidance procedures were repeated at weekly intervals, there was a gradual decrease and, finally, a suppression of levels with each session.

In the case of cardiovascular responses to psychological stress in human subjects—and when more than one physiological measure is taken—such organized patterns also emerge. Using mental arithmetic, performed under duress as the psychological stimulus, Brod produced increases in blood pressure, cardiac output, muscle-blood flow, and splanchnic vasoconstriction in both normotensive and hypertensive subjects. However, it was noticed that there was a trend toward greater renal vasoconstriction and less vasodilation in the muscles of hypertensive subjects. In addition, the hypertensive subjects differed from the comparison group in that after the psychological stimulus had ceased hemodynamic changes and elevations of blood pressure persisted for a longer time. The pattern that Brod and his group demonstrated is probably under the control of the sympathetic vasodilator system.' One of the main relay stations of this system is located in the perifornical hypothalamus that, when experimentally stimulated, produces a complex pattern both of cardiovascular and of behavioral responses. These consist of sympathetic vasodilatation in muscle, increased heart rate, vasoconstriction in the vascular beds (other than muscle) and an increased secretion of

catecholamines. This pattern is analogous, if not homologous, with that described by Brod in man.

This work highlights the need to study much of the behavioral and physiological responses to stress in order to elicit an organized pattern of change. One may then align the pattern with known physiological fact. As exemplified, known patterns of physiological change can be produced by stimulating discrete brain sites—either by relay nuclei or axons that are part of complex neural circuits with different outflow channels.

In so doing, it becomes more apparent that the brain is capable of regulating a whole pattern of physiological change that is mediated by autonomic and hormonal outputs. However, the manner in which the brain does so is largely unknown.

What we are also beginning to realize is that the brain is capable of regulating, with exquisite precision, discrete physiologic change in one or another organ function. To a large degree we owe our awareness of this startling fact about the autonomic outflow to Miller and his pupil, DiCara. Heart rate, systolic blood pressure (independent of heart rate), peripheral vasomotor responses, gastrointestinal motility, and urine formation can be specifically modified in an expected direction by instrumental learning in the curarized rat. They have shown that only the rewarded response changes;

and that the learned response is specific to the type of response that is rewarded, and not limited to general patterns of autonomic discharge.

This work clearly is of great and potential therapeutic importance as well as of great scientific interest. It contains the seed of the possibility of analyzing how such discrete responses are generated in the brain, and how human beings with a disturbance in physiological function can be trained to correct it.

Autonomic and Enzymatic Responses

We have mentioned that Mason found that repeated sessions of avoidance conditioning markedly attenuated and even depressed 17-OHCS levels. From work on human subjects, we know that unexpected or novel situations elicit marked physiological change. The anticipation of a task, or stress, also does this. Where stresses are repeated, a physiological adaptation occurs.

Obviously an important variable in adaptation is the age of the animal, and his previous experience. Early experience also modifies later response tendencies and adaptations to stress.

Presumably, changes in the brain are associated with early experiences, and permanently alter the manner in which later experience is transduced.

Early experiences modify both behavioral and physiological response tendencies. Presumably, therefore, during the course of the transduction of early experience by the brain, permanent changes are produced that modify later responses to stressful or other experiences.

We should like to review some evidence for this contention, and the even more impressive evidence that there are different physiologic mechanisms in the body that are responsible for bodily changes, depending on the duration of the stress.

Very acute stress, preparation for activity, and novel experiences is now known to be divided into anticipatory' and reactive phases that are associated with increases in systolic blood pressure, heart rate, and catecholamine and steroid excretion, etc. In all likelihood these changes are largely mediated neuronally. The mechanism underlying the increase in catecholamines, especially norepinephrine secretion (see Von Euler's Figure One) appears to be due to a sharp increase in norepinephrine synthesis from tyrosine but not Dopa, when an increase in sympathetic nerve activity occurs. However, no increase in tyrosine hydroxylase (TH) activity occurs, so that either no new enzyme is formed or formation is inhibited by norepinephrine.

The absence of change in TH content of tissue during acute stresses or stimulation stands in contrast to the change that is produced by sustained

stress or sympathetic nerve activity.

Thoenen, Mueller, and Axelrod had shown that a reflex increase in sympathetic nerve activity over several days produced a marked increase in TH activity in the adrenal gland of the rat, and in the superior cervical ganglion and in the brainstem of the rabbit.' The activity of phenylethanolamine-N-methyl transferase (PNMT) is also increased. By a number of experimental procedures, Axelrod and his co-workers have shown that the changes in content of these enzymes in the adrenal gland and in the superior cervical ganglion is not only neuronally mediated but depends on the formation of new protein. In other words, they have shown that the increase in TH activity is transsynaptically induced.

The increase of PNMT produced by neuronal activity is, however, also under the control of ACTH. It depends on new protein (enzyme) synthesis and occurs even after hypophysectomy and the administration of ACTH. To a much lesser degree, the two other biosynthetic enzymes, TH and dopamine -hydroxylase, are similarly controlled.

That these changes in enzyme activity with sustained neuronal activity are not only the product of the laboratory is attested to by the exquisite work of Henry and his co-workers. This work confirms the fact that chronic stress produces marked changes in the biosynthetic enzymes of norepinephrine,

but, in addition, it produces correlated changes in blood pressure and renal pathology.

Henry and his co-workers' results have been confirmed by the use of the restraint technic. Further evidence for the dually mediated changes in adrenal enzyme content has been obtained. Other work, using this method, begins to provide insight into some of the possible brain mechanisms mediating these changes.

Restraint of animals is also an excellent method for producing gastric ulcers and, therefore, for working out some of the mechanisms by which stress promotes an anatomic lesion.' Many of the experimental parameters and characteristics of the animals that promote or prevent the development of the gastric lesions have been worked out, and were ably reviewed recently by Ader.

But, one finding is of central importance because it attests to the importance of the interaction of an experience—in this case, restraint—with the state of the organism. Ader' found that his rats were significantly more likely to develop gastric ulcers when immobilized during the peak, rather than the trough, of the activity cycle.

Restraint—immobilization also has potent effects on the peripheral and central content of biogenic amines. Kvetnansky and Mikulaj have shown in

rats that immobilization for ninety minutes produces an increased excretion level of norepinephrine and epinephrine associated with a decrease in adrenal epinephrine (but not norepinephrine) content, which persisted for twenty-four hours after its conclusion. With persistent immobilization, adrenal epinephrine content was unaffected, but norepinephrine content increased, while the urinary excretion of epinephrine remained elevated. These results suggest that the adrenal medulla enhances its ability to replace released epinephrine with repeated immobilization stress. This "adaptation" to stress appears to be due to a neuronally dependent elevation of TH and PNMT in the adrenal medulla. When immobilization is stopped, TH levels diminish with a half-life of about three days.

Following the end of immobilization, there is a latency period of about six hours for levels of TH and PNMT to become elevated. Further elevations of levels occur in the next seven days of immobilization, but after six weeks of daily immobilization no further increases occur.

The long-term increase in catecholamine levels in the adrenal medulla produced by immobilization are not only neuronally dependent but are *also* under the control of ACTH. After hypophysectomy, depletion of adrenal epinephrine levels with restraint is greater than in control animals, and levels of TH and PNMT fall. On repeated immobilization, TH levels but not PNMT in hypophysectomized rats do, however, rise but never to control levels. The

rise in TH levels in operated rats is neuronally dependent in the main, while the rise in PNMT and some of the rise in TH levels depends almost entirely on administered ACTH prior to stress.

On the other hand, serum dopamine--hydroxylase, which transforms dopamine into norepinephrine, was increased after one thirty-minute immobilization of rats, and continues to increase with daily immobilization for a week. The source of this increase is not, however, the adrenal gland but sympathetic nerves.

Immobilization stress of three hours also significantly accelerates the disappearance of radioactive norepinephrine from the heart and kidney. The question of how immobilization stress is centrally translated into these neuronally and hormonally dependent, peripheral changes is unanswered except for some very interesting work by the Welchs. They showed that restraint stress can cause a greater elevation of *brain* norepinephrine and serotonin in mice who previously had spent eight to twelve weeks in isolation when compared to litter mates housed in groups.

This elevation of brain amines occurs despite the fact that the isolated mice have slower, baseline turnover of brain biogenic amines than those housed with others.

This work has several important implications. The isolated mice were

more hyper-excitable behaviorally than the housed controls. In other words, previous experience affected behavioral response tendencies, while the finding of different turnover rates and greater elevations with immobilization clearly indicates that previous experience may lead to individual differences in brain amines as well as in behavior.

Restraint and exposure to cold alone, and in combination, also affect other brain amines. Histamine levels in the hypothalamus and cerebral cortex of rats are depleted significantly in the first two hours of these "stresses." Apparently, there is an initial and marked enhancement of synthesis that cannot keep pace with the rate of release and destruction of the amine, leading to depletion of levels.

The series of experiments that have helped to elucidate the different effects of stress and some of the mechanisms responsible for them add important links in the chain of events in the brain associated with stress.

The Effect of Early Experience on Later Responses to Stress

In reviewing the Welchs' work, it becomes apparent that the earlier experience (isolation) of an animal not only determines his behavior (such as hyper-excitability) but also causes larger elevations of biogenic amine levels in the brain when the animal is restrained. Such data implies that early experiences determine later responses to stress, and thus *provide a beginning*

basis for understanding individual differences in behavioral and physiological response tendencies to stress.

Further evidence for this statement can be found in Henry et ah's paper dealing with responses to the stress of social confrontation with members of the animal's own species in animals with different previous experiences.

They showed that the effects of mixing males from different boxes, of aggregating them in small boxes, of exposing mice to a cat for many months, and of producing territorial conflict in mixed males and females resulted in sustained elevations of systolic blood pressure, arteriosclerosis, and an interstitial nephritis; higher levels of systolic blood pressure were achieved by male rather than by female mice who also failed to reproduce under such conditions. If male mice were castrated minimal elevations in blood pressure occurred, while in those given reserpine minimal decrease in blood pressure resulted. Previous, that is, early experiences of living together attenuated the effects on blood pressure of experimentally induced aggregation and territorial conflict. On the other hand, isolation of animals from each other after weaning and to maturity exacerbated the effects of crowding on blood-pressure levels.

Recently Axelrod et al. and Henry et al. reported that the socially isolated mice showed a decreased activity of TH and PNMT activity in the

adrenal gland in the baseline state. When these animals were now crowded together, the effect was to increase the activity of these enzymes—an increase significantly greater than in those accustomed to crowding.

The activity of both enzymes, of monoamine oxidase, and the contents of noradrenaline and adrenaline in the adrenal gland were greater in these previously isolated animals who were in constant contact with each other than in animals who were conventionally housed, i.e., crowded, but never isolated.

In other words, in the brain amine and adrenal gland enzyme levels of socially isolated animals are lower than in animals housed together, but under stress a marked reactive "overshooting" in activity occurs.

It seems likely, therefore, that responses to stress are, in part, determined by previous experiences. Individual response tendencies are then produced that have their biochemical correlates. The search for the biochemical correlates of individual response tendencies seems to be predicated on the technical development of measuring enzyme levels, rather than the products of biosynthesis. As the work reviewed attests, a substance such as epinephrine can remain at normal levels in the urine despite prolonged or repeated stress, while the relevant enzyme levels in the adrenal gland have increased substantially.

We still do not know very much about how early experiences interact with a schedule of maturational changes in the brain. There is evidence to suggest that permanent changes in behavior or of physiological function regulated by the brain can only be accomplished during “critical” periods of development. We know little about what such periods represent in terms of brain function. In fact, a major, unexplored area of neurobiology is the study of the interaction of experience with the biochemical and physiologic maturation of the brain. For example, there appears to be a maturational sequence for brain biogenic amines; Glowinski et al. showed that after the eleventh day of life, the rat rapidly develops the capacity to excrete norepinephrine and its metabolites with an efficiency approaching the adult. They also showed that the blood-brain barrier to norepinephrine is present at birth.

Endogenous levels of brain norepinephrine rise rapidly in the second week of the rat’s life, so that after twelve days they are only slightly lower than levels at twenty-four days and in adulthood, but are quite noticeably influenced by external factors such as nutrition.

In the future, one might study the effects of separating young animals at different ages on amine, RNA, DNA, amino acid, etc. levels. For example, separating rat pups from their mothers produces significant alterations in brain levels of free amino acids and acetyl cholinesterase in two days.

The work we have just reviewed suggests that physiological responses to stress are, in part, determined by early experience. Generally speaking, in medicine very little attention is paid to the personal (in contrast to the medical) history of the patient prior to hospitalization. Nor is there much inquiry directed at the immediate history of the sick person just prior to his admission. So far we have reviewed recent data on the social conditions in which animals are reared and how these determine later biobehavioral responses. Additional evidence suggests that experiences in intrauterine and early life affect other important physiological systems.

Milkovic and Milkovic have shown that adrenalectomy of the mother rat prior to parturition or unilateral ligation of the fallopian tube prior to conception results in the offspring's being capable of giving an adrenal response to severe stress as early as one or two days after birth. Thoman and Levine have done work that suggests that changes in adrenocortical activity during both prenatal and early postnatal life can affect subsequent patterns of neuroendocrine response in the adult organism. They showed that the newborn rat pups of mothers adrenalectomized prior to conception had hypertrophied adrenal glands and higher plasma corticosterone levels than the offspring of normal mothers. Moreover, as adults these two groups of rats showed different responses to stress, the offspring of adrenalectomized mothers showing significantly higher hormonal levels than the offspring of normal mothers. Thoman and Levine viewed these differences as almost

exclusively due to prenatal effects, since switching the litters of adrenalectomized and non-adrenalectomized mother rats had no effect on the differences in adrenal function in the offspring, despite the fact that adrenalectomized mothers lactate less. Thus, the effects of the maternal adrenalectomy on the offspring must have occurred *in utero.*

There is a large body of evidence on the effects of early life events on the adrenal-cortical response to stress. Levine et al. showed that rats handled as infants had a more marked adrenal-cortical response when exposed to cold in adulthood than did unmanipulated litter mates. This was also true" for rats exposed to a brief electric shock in adulthood after neonatal handling. They observed a significantly greater and more sustained increase in plasma corticoids as compared with unhandled controls, despite the fact that not only were the resting plasma levels of corticoids the same for both groups but the weights of the adrenal glands did not differ. When less drastic stresses were used, neonatally handled rats had a less marked adrenal-cortical response than control animals that had not been gentled. When exposed to an open-field trial for three minutes in adulthood, the handled rats showed some increase in plasma corticoids but significantly less than the control animals. To explain these seemingly inconsistent findings, Levine postulated that one of the major consequences of handling young rats “is to endow the organism with the capacity to make finer discriminations concerning relevant aspects of the environment. The animal then is able to make responses more

appropriate to the demands of the environment including appropriate responses to stress."

Just how these experiences permanently alter the function of the adrenal cortex so that the adult shows a greater repertoire of adrenal responses is unknown. There does appear to be a general acceleration of maturation as a result of handling. Body hair, the opening of the eyes, and the beginning of adequate locomotion appeared from one to four days earlier in the stimulated animal. It is also likely that the onset of puberty was hastened, and that myelinization of tracts in the CNS was accelerated as a result of handling. Early handling of rats altered the responsivity of the pituitary-adrenal-cortical axis. When rats were handled in the first two days of life, an increase in circulating corticoids occurred. Further evaluations were seen when such animals were stressed on the third day of life, i.e., a time in which such animals were once considered to be nonresponsive to stress. Ader demonstrated that early handling or exposure to shock accelerated the maturation of the twenty-four-hour adrenocortical rhythm. Rats reared under twelve-hour alternating periods of light and dark were killed at times corresponding to the periods at which maximum or minimum plasma corticosterone concentrations occur in mature animals. The characteristic twenty-four-hour adrenocortical rhythm was observed to develop at least five days earlier in rats who had been stimulated either by shock or handling.

It has been postulated by two groups of investigators'' that the control of the endocrine system in the adult is partially accomplished by a feedback mechanism or "hormonostat." This mechanism would constantly "monitor" levels of plasma corticoids, compare these levels with a controlling "set point," and adjust ACTH secretion according to the plasma level. The crucial feature of this regulatory system requires that the "set point" not be fixed, but rather that it varies according to the metabolic demands placed upon the organism. Since the sensitivity of such a regulatory mechanism could be determined by a number of variables, among which are stressful early experiences during a critical period of development, it is possible that early experiences may allow for more graded and versatile responses. This could explain why stimulated rats showed a moderate increase in steroid output when placed in an open-field situation, and a large and rapid increase when subjected to electroshock. Unstimulated animals tended to react hormonally in a more stereotyped way, with large increases in hormone levels in response to change because of a more limited "hormonostatic" repertoire.

Sensory input to the brain, from handling, for example, may alter its maturation. (Obversely, sensory deprivation may impair levels of neurotransmitter substances in the brain.) In 1933, Langworthy observed that visual stimulation accelerates myelinization in the optic tracts of premature and term infants. Other workers' have shown that a flashing light in a cat's eye will increase the blood flow, temperature, and metabolism

specifically in the occipital cortex, lateral geniculate body, and optic radiations, while olfactory stimulation produced similar changes in the olfactory cortex. Dehydration, a stimulus to antidiuretic hormone secretion, has been shown to cause a large increase in the ribonucleic acid and acetyl cholinesterase contents of the supraoptic and paraventricular nuclei of young rabbits.

In other words, early experience, including sensory stimulation, affects a wide variety of brain mechanisms. Much is now known about the mediating role of the hypothalamus in the release of pituitary hormones. Inputs to the hypothalamus from sensory pathways from the thalamus and basal ganglia and limbic systems are recognized. The neural mechanisms for the integration of a variety of hormonal and neural inputs are to be found in the hypothalamus.

In fact, one may infer from Mason's work on the effects of stress on a variety of hormones that hypothalamic mechanisms exist that are responsible for the regulated release of most hormones.

Admittedly, most of the attention in the past two decades has been focused on the secretion of cortisol by the adrenal cortex, which secretion is the final step in a series of processes probably beginning in the cerebral cortex and involving the limbic system, the hypothalamus, and the pituitary

gland. As a result of this work, new concepts about the relationship of the CNS to the endocrine system have developed. It is believed that the brain and the endocrine glands comprise a thoroughly integrated system that coordinates the organism's responses to alterations both in its external and internal environment. Under the influence of stressful stimuli, a sequence of events is believed to occur that terminates by the activation of hypothalamic "transducer" cells. These cells respond to neural input by the release of a putative, amine transmitter with the release of a polypeptide, similar to pitressin in structure. This polypeptide is called the corticotropin releasing factor (CRF). CRF reaches the anterior portion of the pituitary gland via the portal-venous system around the hypophysial stalk at the median eminence, and ACTH is released to stimulate the adrenal gland to produce cortisol. The degree to which the system is activated may depend upon the degree of stress and its duration. Despite the fact that a negative "feedback loop" exists between the adrenal cortex and the anterior pituitary, mediated by circulating levels of cortisol, persistent neural input will result in the continued release of CRF and ACTH despite elevated cortisol levels. Individual differences in animals in the nature and duration of the cortisol response to stress may be due to early experiences. Mason and Hamburg have observed individual differences in 17-OHCS excretion in man that are consistent over months and through several stressful experiences. These individual differences consisted of variation in the range of fluctuation of 17-OHCS

under normal circumstances and in response to disturbing or stressful stimuli. Genetic factors may also play a role in producing such individual differences.

The mechanism outlined for the control and regulation of ACTH and cortisol seems also to apply to other trophic hormones of the pituitary. For each hormone, releasing factors are postulated or have been identified. These are not only subject to end-product inhibition but are under neural control by inputs from the limbic system, cortex, and thalamus. Furthermore, inhibiting factors, besides releasing factors, have been postulated in the case of trophic hormones. In addition, trophic hormone release is affected by sensory input —ovulation in some female animals only occurs after vaginal stimulation. Trophic hormone release in some cases is rhythmic: The pulsatile release of ACTH is greatest in the early hours of the morning, concomitant with the last rapid eye movement period of sleep. In some mammals, oestrus is likewise influenced by environmental light. The mechanism of this influence is known —it entails the suppression of oestrus by melatonin synthesized in the pineal gland during periods of darkness.

It has been amply demonstrated that the gonadal hormones influence the brain during critical periods of development, helping to determine the sexual and reproductive behavior and pituitary-gonadotrophic function in the adult animal. Harris and Young hypothesized that the sexually

undifferentiated brain is “organized” by gonadal hormones during fetal and early neonatal life. Subsequently, several investigators have shown'' that the presence of androgens in small amounts during the first five days of life in female rats alters the regular cycle of gonadotrophin release to an aperiodic one. In the absence of any gonadal hormones, the gonadotrophins are secreted cyclically. Thus, the absence of androgens in the male rat in the first forty-eight hours of life results in the cyclic elaboration of gonadotrophins. In addition, the neonatal castration of a male rat drastically alters his sexual behavior. When injected with low doses of estrogens and progesterone’s as an adult, he exhibits the complete repertoire of female sexual behavior. Castration of adult males and similar treatment with estrogen and progesterone does not yield such results. It is apparent from these data that during a critical period in early development androgens acting on the brain are responsible for the acyclic secretion of gonadotrophins. They determine male sexual behavior in much the same way that they affect the development of male sexual morphology. It is evident, therefore, that sex hormones in early life play a major part in determining sexual behavior, morphology, and physiology. It is possible also, as Levine has pointed out, that the adrenal corticoids may have a profound effect upon the organization of the brain and may influence a number of functions associated with neuroendocrine regulation of ACTH.

Varying early experiences also influence immune responses. Friedman

et al. have shown that the effects of early experience on immunity vary depending upon the challenging agent and at what time during the host's life it is applied as well as on the genetic strain of the animal. They exposed groups of mice to periodic, paired light shock, periodic light and aperiodic shock, and periodic light without shock. They found that the animals subjected to the first of these conditions developed a high rate of infection on exposure to Coxsackie B-2 virus, as compared with the other groups and with matched controls. Ordinarily, this strain of mice is highly resistant to this virus. Yet exposure to Coxsackie B-i virus, a strain to which these animals are usually very susceptible, resulted in no significant difference in morbidity or mortality between groups. Inoculating stressed mice with *Plasmodium berghei* resulted in a decreased susceptibility and mortality. Ader and Friedman have demonstrated similar variations in response in mice implanted with Walker sarcoma. These animals were either handled or given a three-minute period of electric shock before weaning. When they were forty-five days old, they were injected with a standard dose of Walker sarcoma. The animals handled throughout the preweaning period (three weeks) showed a retarded rate of tumor growth. The mortality rate was higher for them only in the first weeks of life; there was no difference in mortality between the animals handled later in the preweaning period and unhandled controls. Mice who received electric shock in the first week of life had a higher mortality rate than other groups, but animals shocked

throughout the preweaning period or during the third week only had a lower death rate than other groups of mice, including unshocked, control animals. Thus, the effects of early experiences of this kind upon resistance to Walker sarcoma depend upon the nature of the experience and the time during early life when it occurs.

Psychobiological Studies in Animals Relevant to the Etiology and Pathogenesis of Some Medical Illnesses

Observations of patients have led to the formulation of the role of psychological factors in the etiology and pathogenesis of disease. To test the validity of the hypotheses derived from such studies and to work out the mechanisms postulated, studies of animals have been used. Such studies have been successful where research in the clinic has been less than reliable. For one thing, animal studies have added scientific evidence to the claim that environmental stimuli and a wide range of experimental variables do, in fact, produce physiological or structural changes analogous or homologous to clinical disease. Secondly, the postulate that social stimuli may act via the nervous system to alter bodily functions has been strongly supported if not substantiated by such work.

To summarize the achievements of animal studies reviewed up to this point: much is now known about the kinds of behavioral, endocrine, and autonomic changes that conditioning techniques, restraint, or separation may

bring about, and how these alter target-organ structure and function. On the other hand, too little is as yet known about two central issues: (1) sufficient data have not yet been accumulated on the neural circuits and the neuronal and neurochemical mechanisms that mediate social stimuli and instigate autonomic and endocrine changes and are modified, in turn, by feedback from the interior of the body; and (2) we do not know enough about the genetic and experiential factors that presumably, make vulnerable the particular molecular and cellular configurations that terminate in a disease in one target organ rather than another.

Animal studies in this area have two distinct advantages over human studies. First, pure genetic strains of animals can be bred—strains that have a particular sensitivity, e.g., to salt ingestion that produces hypertension or to restraint that produces gastric ulceration. Second, the early experiences of animals can be manipulated to diminish or enhance their susceptibility to later experimental manipulations.

In four instances we present representative data of diseases or disturbed functioning to support these claims.

Gastric and Duodenal Ulcer

Gastric ulcers can be produced in animals by a wide variety of experimental manipulations—i.e., burns, intense sensory stimulation, the

administration of drugs, brain stimulation, diet, restraint or immobilization, and conditioning techniques—used singly or in combination.

When restraint is used, the important parameters are the species and age of the experimental animal, the length of time he is immobilized, and the availability of food and water. The experimenter must also bear in mind that different experimental manipulations may produce gastric erosion in different parts of the stomach and may, therefore, be mediated by different physiological mechanisms that are still unidentified.

Another important experimental variable to be considered is that some animals are more susceptible to a particular manipulation than others. As is true of man, a high level of serum pepsinogen (on a statistical basis) may be assumed to constitute a biological indicator of an increased susceptibility to erosion in the glandular portion of the animal's stomach.

Ader's experiments with rats have particular relevance for our understanding of gastric and peptic ulcers. Specifically, Ader bred rats for susceptibility to gastric lesions on restraint. These animals had higher levels of serum pepsinogen prior to restraint: high serum pepsinogen levels were not, therefore, a response to restraint. In addition, these lesion-susceptible rats manifested some interesting behavioral characteristics. They were more reactive emotionally, and appeared to dominate non-susceptible animals with

whom they were paired in a "competitive" task for water. On the other hand, when these susceptible animals were "handled" early in life, they were less likely to develop gastric lesions on restraint than were the non-susceptible rats who were not handled early in life. Investigators who used other experimental manipulations reached the same conclusion. Life experiences in infancy—such as early weaning —may also be a critical variable in a predisposition to gastric ulceration when male rats are later exposed to conflict situations or to immobilization.

Workers in this field have also used approach-avoidance-conflict situations to produce ruminal ulcers in rats. Lower found that a somewhat different manner of inducing conflict caused ulceration in the glandular portion of the rat's stomach.

Finally, there are the "executive-monkey" experiments, which were done at Walter Reed Army Institute of Research in the late 1950s. It will be recalled that at autopsy ulceration in both stomach and duodenum occurred only in the executive *Macaca iris,* and not in his yoked control.

We have reviewed these animal studies rather selectively in order to highlight the complexity of the social and physiological variables involved and their interactions. However, and despite the parsimony of the data presented, one indisputable conclusion emerges: many of the doubts generated by

"psychosomatic" research on humans in the mind of the critical reviewer, are dispelled by research on the production of ulcers in animals. A number of laboratory experiments and behavioral characteristics (such as activity cycles) do seem to combine with physical stimuli and genetically determined physiological factors to produce gastric ulcers. Moreover, despite the fact that the relationship of gastric ulceration in the rat to duodenal ulceration in man is unclear, duodenal ulceration was produced in monkeys in Brady's experiments.

One may also conclude from these studies that a number of different experimental conditions produce the same anatomical lesion, presumably through some common mechanism. The studies conducted by Levine and Senay are relevant in this connection. These investigators found that when rats were restrained in a cold climate, intragastric pH fell and ulcers appeared. However, an antacid protected against the production of ulcers under such environmental conditions. Presumably, then, these ulcers were caused by an increase in gastric acidity, which is believed to be mediated by histamine. Interestingly, Levine and Senay also demonstrated that restraint and cold increase the activity of histidine decarboxylase, which increase is positively correlated with the incidence and severity of stress ulcers. The inhibition of diamine oxidase (the enzyme which catabolizes histamine) has the same effect.

The work of Levine and Senay raises several interesting questions: By what mediating mechanism do stress and cold induce an enzyme or enhance its activity? Is it a neural or an endocrine mechanism? If it is a neural, what brain mechanisms mediate such an effect? The answers to such questions could be sought by available neurophysiological techniques. In fact, a restrained rat might be a particularly good experimental animal to use for exploring the central nervous system (CNS) by such techniques as chronic unit recording.

Essential Hypertension

Animal studies relevant to the pathogenesis of essential hypertension are notable for their diversity.

In animals, both "simple" and complex stimuli produce elevated levels of blood pressure. "Audiogenic" hypertension has been produced in rats by daily exposure to air blasts. Pickering quotes a Russian experiment in which a male monkey developed elevated arterial pressure after his mate was taken away and he could observe her caged with another male monkey.

But the most convincing and systematic study of the role of complex stimuli in producing prolonged systolic hypertension in mice has been reported by Henry et al. (see page 854). Finally, an interstitial nephritis was found in animals with severe hypertension at autopsy.

Stress of the kind used by Henry can set into motion a number of physiological changes. As we mentioned earlier, Thoenen, Mueller, and Axelrod' showed that a reflex increase of sympathetic nerve activity transsynaptically induced enzyme activity in the adrenal gland after from one to three days. However, others have also shown that social stimuli may increase levels of adrenocortical steroids, constrict renal vessels, and alter levels of brain norepinephrine.

In another area of investigation, salt was found to play a role in the pathogenesis of hypertension; the precise nature of this role has been hotly contested, however. To summarize these findings, various steroids produced experimental hypertension in animals only in the presence of salt. When hypertonic saline was the only source of fluid, hypertension was produced in a variety of animals. The chronic ingestion of too much salt produced hypertension in the rat, but it took time and even then hypertension was not found in all the animals of a particular strain.

In this connection Jaffe and his co-workers have reported that there are two genetic strains of rats. One is resistant and the other is sensitive to salt ingestion. Even a diet containing only 0.38 percent salt caused the rats in the sensitive group to have higher blood pressures (134 mm. Hg, mean) than the resistant ones (112 mm. Hg, mean). In fact, resistant rats on a diet of 8 percent salt showed no blood pressure increases, but the blood pressure of

those who were sensitive to salt rose to 210 mm. Hg, and they developed moderate to severe lesions of the kidneys. Moreover, even the sensitive rats on a low salt diet showed changes in the musculo-elastic, arteriolar pads. This anatomical lesion is thought by these authors to be genetically determined.

In human populations there is a linear correlation between salt intake and the incidence of hypertension: If the intake of salt is low in a group, the probability of some members of that group developing hypertension is lower, and vice versa. In part, the amount of sodium in a diet is culturally determined, of course. However, a craving for salt, independent of requirement and cultural influences also seems to exist in individuals. Little is known about the variable responsible for such a craving. Furthermore, to the best of our knowledge, no attempts have been made to study the psychological factors that might influence man's appetite for salt, and might, therefore, play a role in producing hypertensive disease. Clearly, in the absence of such data, it behooves the worker engaged in research on the psychosomatic aspects of essential hypertension to control salt intake in his subjects. Once again, to the best of our knowledge, this control has not been built into the design of studies conducted to date.

The third line of evidence implicating sodium and its metabolism in essential hypertension was the finding that hypertensive animals have an increased natriuresis and diuresis to salt and water infusion. In addition, the

sodium content of the arterial wall may be increased in such animals.

The fourth line of evidence implicating salt —and specifically the sodium ion—is proven by the fact that the amount of renin extractable from the kidneys of hypertensive rats was proportional to salt and water intake. As renin disappeared from the kidney, the rats showed an increased sensitivity to injected renin. In depleting the kidney of renin, salt probably acts through the medium of an increased plasma volume. Unfortunately, however, the increase of blood renin (and the decrease of kidney renin) in response to the increase in blood sodium does not parallel the increase in blood pressure.

The question of whether psychosocial stimuli elicit circulatory responses has been answered, in part, by the use of conditioning procedures. Experimentally induced general behavioral changes, such as fear, are particularly likely to evoke an increase in unconditioned responses in animals. Conditioned cardiovascular responses, including elevations of blood pressure, can be retained in animals for many years, even after the original and concomitant motor or salivary responses can no longer be elicited.

Direct brain stimulation can serve either as the conditional stimulus or the unconditional stimulus. Motor cortical area stimulation (as an unconditional stimulus) that does not produce movements leads to vasoconstriction or dilation; parietal stimulation leads only to constriction.

One of these areas may be the locus for applying a conditional stimulus, another for an unconditional stimulus to produce vasoconstriction. In dogs hypertension developed, became more severe over a period of months, and then remained elevated despite the fact that the conditioning procedures had been stopped. Even renal changes were observed after hypertension was produced by such means. Finally, of particular interest is the fact that the animals studied showed individual differences in blood-pressure responses.

The studies described above used "classical" conditioning procedures. When avoidance techniques were used in experiments with monkeys, the introduction of avoidance schedules for a period of fifteen days caused an initial acute increase in blood pressure and pulse rate. The animals were then placed on a continuous avoidance schedule, and thereafter the change in blood pressure depended on the length or complexity of the schedule. In those monkeys on the more complex schedules, blood pressure remained as high in the intervals between lever pressing sessions as it had been during the experimental sessions. Increases of systolic and diastolic pressures occurred, regardless of the kind of schedule, when avoidance conditioning was carried out over a seven-to-fourteen-month period. But once the initial acute elevations of blood pressure mentioned in Forsyth's first paper had subsided, it took about seven months (during which Forsyth and his colleagues worked twelve hours a day) for the rise in blood pressure to occur. Interestingly, behavioral changes, in the form of excitability and increased activity, also

occurred. Pressor responses that had been neutral prior to training were observed in the presence of a variety of stimuli. Only one point has not been made in this report: we do not know whether the elevated pressures persisted after the avoidance performance had ceased. We have indicated that no single psychological or physiological variable can account for the pathogenesis of essential hypertension. This statement is further attested to by an interesting set of observations made by McCubbin. After very small doses of angiotensin (which had no immediate effect on blood pressure) had been infused into dogs for several days, their arterial pressure became elevated and labile. (Before the infusion the mean arterial pressure had been steady.) When the dogs were surrounded by normal laboratory activity, their blood pressures were labile and high. If the laboratory was quiet, even minor distractions caused marked further increases in blood pressure, due to abrupt increases in peripheral resistance. When these dogs were sensitized with an infusion of tyramine, which releases endogeneous stores of norepinephrine, further elevations of blood pressure were produced. Infusions of norepinephrine had no effect on blood pressure. These observations suggest that a systematic study could be carried out of the role of psychosocial stimuli in animals made hypertensive by small doses of infused angiotensin. Extrapolating from recent work on the pharmacological effects of angiotensin, it might be possible to test the hypothesis that angiotensin sensitizes the brain to sensory input as well as having effects on blood pressure through the

medium of the brain.

Recently, Scroop and Lowe and Ferrario et al. found that dogs anesthetized with chloralose responded to the infusion of angiotensin into the vertebral artery in doses too small to affect the systemic circulation directly. As a result, there was an increase in heart rate and arterial blood pressure, and a fall in central venous tone. These effects were thought to be due to an increase in cardiac output without change in peripheral resistance. But the fact that these hemodynamic changes were abolished by vagotomy suggest that the infused angiotensin stimulated medullary centers to reduce vagal tone. Admittedly, with the exception of the increase in arterial pressure, the changes in cardiovascular function reported are not typical of those found in essential hypertension. Nevertheless, the possibility that angiotensin may act through the CNS is of interest, especially as it has now been shown that it also causes anterior hypothalamic neurons to fire. In addition, evidence has recently been presented that the brain may form angiotensin by virtue of an unidentified enzyme it contains.

As was true of peptic ulcer, the evidence derived from animal studies on essential hypertension is much more convincing than that derived from human studies. Blood pressure, vasomotor tone, and many of the physiological variables implicated in the pathogenesis of hypertension in man can be related to naturally occurring events and to animal behavior

manipulated in the laboratory. In fact, the recent evidence of Miller and Mason raises the exciting possibility that we may be on the verge of a real breakthrough in understanding the pathogenesis and pathophysiology of hypertension. Moreover, by a combination of techniques, the answers to the three central questions delineated earlier might be sought in studies of animals. This possibility justifies the restatement of these questions: (1) Can renal blood flow be increased in one renal artery and decreased in the other by operant conditioning? If so, the content in each renal vein of renin and/or angiotensin II could be measured; (2) Can the distribution of blood flow within each kidney (measured by intra-arterial injections of Krypton and intravenous injections of Iodoantipyrine-I 131) be affected differently by different operant methods? And (3) If renal blood flow can be diminished by operant conditioning procedures, does hypertension ensue? Some of the mechanisms that mediate these events remain unknown.

Stressful Influences on Cardiac Rhythm and Their Mechanisms

Ectopic activity of the heart beat has been recorded in stressful situations and can be produced experimentally by stimulating either the vagus or the sympathetic cardiac nerves. When both are stimulated simultaneously, ventricular extrasystoles can be produced. Stimulation of the posterior hypothalamus can elicit a similar arrhythmia in cats under chloroform anesthesia. While stimulation of the posterior part of the lateral

hypothalamus and the mesencephalic reticular formation regularly causes a profound tachycardia as well as raising the blood pressure—both phenomena outlast the duration of the stimulus.

In all likelihood, the effects on rhythm of such brain stimulation are mediated both by the vagus and cardiac sympathetic nerves. Therefore, arrhythmias of various kinds can be produced in animals whose heart is intact by means of brain stimulation.

When the heart is damaged, as for instance by coronary artery ligation, ventricular fibrillation can be prevented only by total denervation of the heart. In the obverse experiment, ventricular fibrillation could be produced in some dogs by hypothalamic stimulation following coronary artery ligation.

Neither the exact mechanism of arrhythmia nor the pathways mediating the effects of brain stimulation leading to the vagus and cardiac nerves from hypothalamic centers have been fully worked out.

It is also of interest that heart rate and rhythm can be affected by psychological means. Heart-rate changes can be produced by instrumental learning in animals and man, and arrhythmias decreased by these means.

Thyroid Disease

In contrast to the large number of animal studies of gastric ulcers, few systematic studies have been done in the field of thyroid disease despite the relatively large number of available tests for thyroid function.

A rise in plasma protein-bound I consistently occurred in sheep exposed to barking dogs. The reverse effect on thyroid function was obtained when rats were exposed to the sight of a larger, fierce wild rat through a glass screen. Two explanations have been advanced for this response. Some authors believe that corticosteroids inhibited the release of I from the thyroid gland; others contend that secretion of the hypothalamic corticotrophin releasing factor resulted in the diminution of the thyrotropin releasing factor (TRF). The mediating role of TRF between social stimuli and enhanced thyroid function is a source of considerable controversy. However, Mason found that plasma-thyroid-hormone levels showed a slow but prolonged elevation concomitant with a three-day avoidance session in monkeys. This elevation of hormone levels began during the avoidance session, and lasted for two or three weeks after termination of the schedule. The finding that electric stimulation of the hypothalamus enhances thyroid function in several species of animals has been well documented, and various limbic-area structures have also been implicated in the regulation of thyroid function. Finally, norepinephrine and epinephrine are known to activate thyroid function, and are, of course, acutely responsive to psychosocial stimulation.

However, thyrotropin may not be an important factor in thyrotoxic disease because it is believed today that a long-acting thyroid stimulator (LATS) rather than thyrotropin, is the pathogenetic agent in Graves' disease. LATS is an immunoglobulin. Therefore, the logical question arises as to how the nervous system could contribute to its regulation; or, putting it another way, in addition to the exposure to an antigen, do other factors control antibody formation or contribute to the action of an antibody? At this point, one can only speculate that there may be genetic factors that influence antibody formation in thyroid disease, and that LATS may act on cyclic AMP (adenosine monophosphate) as the corticosteroids and catecholamines do, to promote the entrance of iodine into thyroid cells. In addition, it is known that adrenalectomy and the administration of thyroid hormone enhance antibody formation, and that the nervous system may regulate immune responses. For example, avoidance conditioning influenced immunological responses. At the same time, some evidence has been accumulated that indicates that midbrain and hypothalamic (tuberal) lesions could protect guinea pigs against anaphylactic shock. Anterior hypothalamic lesions were significantly more successful in protecting rats against anaphylaxis to ovalbumin than were posterior hypothalamic lesions. Anterior hypothalamic lesions lowered circulating antibodies to the same antigen in guinea pigs and made them less sensitive to toxic doses of histamine, possibly by modifying the physiological reactivity of the bronchiolar tree to the constrictive effects of histamine.

In summary, animal studies have provided rather reliable evidence on several scores: target-organ change and physiological responses occur that are relevant to the diseases under consideration in this paper. Furthermore, one may now conclude, on the basis of Mason's work in particular, that avoidance conditioning does indeed act through the CNS to produce changes in a series of hormones, including such critical ones as corticosteroids, catecholamines, aldosterone, plasma-thyroid hormone, growth hormone, plasma insulin, and sex hormones. Furthermore, these studies have given rise to generalizations that these hormonal changes are patterned and do not occur individually. Nor are these patterns of change unique to avoidance conditioning: they occur with novel stimuli as well.

Such patterns of change also occur in the autonomic system, as evidenced, for example, by the cardiovascular changes that precede and accompany exercise. Whereas these adjustments were once considered to be instigated exclusively by peripheral mechanisms, Rushmer has postulated that the onset of vasodilation and increased flow in muscle, heart rate and output, etc. at the start of exercise emanate from the nervous system as an autonomic concomitant to the muscular activity under volitional control.

In other words, concomitant patterns of cardiovascular and motor activities exist. These cardiovascular adjustments seem to be specific to a given behavioral activity; other adjustments probably occur with other

activities: For example, in preparing to fight another cat, cats showed bradycardia, a decreased cardiac output, and vasoconstriction in the iliac and mesenteric vessels. But when actually striking the other cat, the heart rate and cardiac output rose, the iliac bed dilated and the mesenteric bed constricted. In neither case was there a significant rise in blood pressure, however.

Clearly, these findings require further clarification. A contradiction appears in the work on the production of gastric ulcers in rats—Mason's work and the work mentioned above on cardiovascular changes. On the one hand, different psychosocial stimuli or situations were found to produce the same anatomical lesion or pattern of physiological change; on the other, they produced different changes. Immobilization restraint invariably produces lesions in the glandular portion of the rat's stomach, but conflict situations produced ruminal lesions in some rats, and glandular lesions in others.

Is this discrepancy a function of strain differences? Or can it be attributed to quantitative or situational factors, or differences in mediating physiological mechanisms? Only further research will provide the answers to such questions. Other interesting questions remain unanswered as well: At what thresholds do avoidance schedules produce the requisite changes, as measured by the animal's ability to escape, the predictability of his response, and the intensity and duration of stimuli?

Conclusion

We have attempted to demonstrate that many physiological parameters are influenced by environmental factors and that disease states may be produced by experimental manipulations of animals. There is increasing evidence from a review of the literature that many integrative physiologists are beginning to be aware of the fact that certain broad generalizations no longer hold. The autonomic nervous system is no longer viewed as mainly responsible for the maintenance of the "constancy" of the internal environment, or as separate from the endocrine system. (For a review of modern data and concept about the autonomic nervous system, see Volume 4, Chapters 22 and 23, of the *Handbook).* We regard the autonomic nervous system today as one of the three principal output systems of the brain that are involved in the mediation of the brain's responses to stimuli of environmental origin, including preparation for activity in response to an outside stimulus. These responses are imposed on continuous, ongoing, autonomic discharge, which varies according to the behavioral state of the organism. In the state of rapid eye movement sleep, for example, *variability* of heart and respiratory rates, blood pressure, etc. is much greater than in slow wave sleep or quiet wakefulness. In other words, autonomic discharge is phasic during this behavioral steady state.

The autonomic nervous system is both responsible for and under the

influence of hormonal output. The endocrine system, in turn, is the second major output system of the brain mediating environmental change. In fact, there is an increasing realization of the close interactions of hormonal and autonomic mechanisms.

The classical view of autonomic function was largely obtained by analytic experiments in which only a single input (such as blood-pressure change) was varied while inputs from many other afferent zones were either eliminated or held constant. Only when the organism is studied as a whole, in an integrative manner, does it become obvious that a change in one variable (such as carotid-sinus pressure) interacts with other inputs to the brain as well as giving rise to a multiplicity of effects such as decreased adrenal-catecholamine-antidiuretic-hormone production as well as cardiac-reflex slowing, decreased cardiac-sympathetic activity, and splanchnic-bed vasodilatation, etc. All these effects must be mediated by widely disparate circuits in the brain.

These advances in physiological data and concepts must be made available to the behavioral biologist while medicine must incorporate the contributions of behavioral biology. For example, it is generally recognized that genetic factors play some role in the etiology of essential hypertension, Graves' disease, and probably in peptic ulcer. But we have not yet determined how much of the etiologic variance can also be attributed to experiential (e.g.,

social, familial, and economic) factors. Methodologies have been developed that would allow the investigator to determine the relative contributions of genetic and experiential factors in the etiology of disease.

At present, in the case of hypertension, about one-third to one-quarter of the variance is ascribed to genetic factors. That familial factors may play a role is attested to by the fact that spouses tend to share similar blood-pressure levels in proportion to the duration of the marriage. Further, the parent-child correlation of pressures tends to be greatest in families in which spouse aggregation is demonstrated. But what could be the factors in the environment of family groupings capable of influencing their blood pressure? Some recent work suggests that if familial factors play a role in elevated blood pressure, they are established early in life. Only future research can determine the nature of these familial factors.

On the other hand, by extrapolating from the work done on animals by Ader and Mason (see von Euler's Figure i], one is led to the inevitable conclusion that these many diseases (such as hypertension and ulcers) are neither caused nor sustained by any single pathogenetic or pathophysiological factor. Rather, psychosocial stimuli, acting through the nervous system, activate a wide range of interrelated, integrated responses. In essence, the nature of the factors involved, the changes they undergo in the course of the disease, and their interrelationships attest to the fact that many

diseases are primarily diseases of physiological regulation. Similar statements have been made by Brooks, Harvey, Menguy, and Ryss and Ryss. In the past, clinical psychobiological research consisted primarily of psychoanalytic observations and single dependent variables studied by psychophysiologists. Psychophysiological results were then conceptualized in linear causal terms. For example, "anxiety" caused an increased heart rate.

It is not enough to state that many important diseases are diseases of regulation in which the nervous system participates. The specific nature of the disturbance in regulation must be specified: Admittedly, it is difficult to conceptualize such regulatory patterns. But control-theory models and models derived from molecular biology do exist.

For example, in molecular biology various kinds of regulatory devices are known: (1) In enzyme synthesis, enzymes may be formed ("induction") only in the presence of substrate. (2) Enzymes in a biosynthetic pathway may be repressed by an excess of the end product of the pathway ("feedback inhibition"). (Jacob and Monod have attributed these two types of regulation to a regulator gene. In the proper configuration, the product of the gene acts on another area to inhibit expression of one or more genes in an adjacent area. Other regulatory devices have been described as well.) (3) In enzyme activity, the initial enzyme in a biosynthetic pathway is usually the one inhibited. (4) There is usually more than one initial enzyme in a common

biosynthetic pathway. These act in conjunction and catalyze the same chemical reactions, but are subject to different feedback regulation. And (5) in protein synthesis, regulation is achieved at the rate at which the initial step in the synthesis of the protein chain occurs, and not at the rate of enzyme synthesis. Other forms of molecular regulatory activity, though carefully conceptualized, do not fit any of the five models mentioned above. And regulation of excitation at the synapse may also take different forms, most of which are well known.

These concepts have important implications for a theory of medicine, with particular emphasis on theories of etiology and pathogenesis of disease. At the same time, they may help to incorporate data that suggest that stressful experience plays a role in the etiology and pathogenesis of disease.

In turn, we would suggest that the information we have reviewed has implications for the practice of medicine and the education of students and physicians. Thus, it may be economically more expeditious and technically more feasible to isolate a patient completely from other human beings in an intensive-care unit, but the psychological effects of isolation, or the impact of a patient watching his own irregular or faltering heart beat on an oscilloscope, may be much more stressful than having him share a room with others with whom he can talk about his real and imaginary concerns.

We believe that the organismic and integrative approach to medicine and disease implied in this chapter can be translated into the teaching of students. Space does not permit a detailed plan for such a curriculum, which one of us has outlined elsewhere.

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Notes

1For a full discussion of this point of view, see Rapaport.